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**Faculty of Medicine**

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**Evaluation of Serum Uric Acid Levels at Sudanese Hypertensive  
patients in Khartoum State (March to July 2019)**

**A thesis submitted for partial fulfillment of requirements for the  
degree of MSc in human physiology**

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

## *Dedication*

*To my father professor Abdulateef Saeed who always support me and love me. To my lovely sweet mother who always stand behind me, support me and pray for me. To my brothers and sisters with my respect and love. And to the soul of my little brother ( Abu obaida) may Allah bless him.*

## *Acknowledgement*

*I would like to extend my thanks and gratitude to all who helped me in completing this thesis . I would like to begin with my supervisor Dr. Mohamed Elshiekh for his invaluable advice, support and continuous observation.*

*I am particularly indebted to my teachers in Department of Physiology, Faculty of Medicine, International University of Africa, for their continuous encouragement and effort.*

## ***Abstract***

**Background:** High Uric acid level has been found to be associated with hypertension; the aim of this study was to evaluate relationship between serum uric acid concentrations with blood pressure measurements in sudanese hypertensive patients living in khartoum state.

**Methods:** A case control study was carried out in Khartoum State; from march 2019 to july 2019. A total of 54 hypertensive patients were taken up for study that satisfied the inclusion and exclusion criteria. Similarly, 54 age and sex matched subjects were kept as control. Blood pressure and anthropometrics parameters were measured and serum uric acid level was evaluated using URICASE/POD/End point Essay.

**Results:** This study demonstrated that there was significant association between uric acid level with both components of blood pressure systolic and diastolic. Furthermore, serum uric acid levels were significantly higher in non-elderly subjects ( $< 50$  yrs) compared with elderly subjects ( $> 50$  yrs) in hypertensive case. In addition, the result documented that there was significant association between uric acid level and duration of HTN. There was no significant difference in level of uric acid with BMI categories in case participants compare to control group.

**Conclusion:** In conclusion, This study demonstrated that there was significant association between uric acid level with both components of blood pressure systolic and diastolic. Furthermore, our data showed that serum uric acid levels were significantly higher in non-elderly subjects (< 50 yrs) compared with elderly subjects (> 50 yrs) in hypertensive case. In addition, The result documented that there was significant association between uric acid level and duration of HTN.

## المستخلص

هناك علاقة بين حمض اليوريك و إرتفاع ضغط الدم. الهدف من هذه الدراسة هو تقييم العلاقة بين تركيز حمض اليوريك و قياسات ضغط الدم عند مرضى إرتفاع ضغط الدم. تمت هذه الدراسة في ولاية الخرطوم في الفترة ما بين مارس 2019 و حتى يوليو 2019.

شارك في هذه الدراسة عدد ٥٤ شخصا من مرضى إرتفاع ضغط الدم بعد استيفائهم شروط المشاركة في هذه الدراسة. و كذلك شارك عدد أربعة ٥٤ شخصا لهم نفس الخواص العمرية و غير مصابين بمرض إرتفاع ضغط الدم و هم (عينة مقارنة).

تم قياس ضغط الدم و قياسات الوزن و الطول و كتلة الجسم و تركيز حمض اليوريك و كانت النتائج تنص على أن هناك علاقة واضحة بين تركيز حمض اليوريك و إرتفاع ضغط الدم، و أن تركيز حمض اليوريك عالي عند من هم أعمارهم دون الخمسين بالمقارنة مع من هم أعمارهم فوق الخمسين و ذلك عند مرضى إرتفاع ضغط الدم. و أيضا تنص النتائج على أن هناك علاقة بين تركيز حمض اليوريك و المدة الزمنية للإصابة بإرتفاع ضغط الدم. ليس هناك فرق في تركيز حمض اليوريك تبعا لاختلاف مؤشر كتلة الجسم عند مرضى إرتفاع ضغط الدم مقارنة بالعينة المقارنة.

الخلاصة أن هناك علاقة بين تركيز حمض اليوريك و ضغط الدم ، و أن تركيز حمض اليوريك اعلى في من هم دون سن الخمسين بالمقارنة بمن هم فوق سن الخمسين من مرضى إرتفاع ضغط الدم، و أن هناك علاقة بين تركيز حمض اليوريك و مدة الإصابة بإرتفاع ضغط الدم.

## Abbreviations

<b>ATT</b>	<b>Anti tuberculous treatment</b>
<b>ACE</b>	<b>Angiotensin converting enzyme</b>
<b>BP</b>	<b>Blood pressure</b>
<b>BMI</b>	<b>Body mass index</b>
<b>CVD</b>	<b>Cardiovascular disease</b>
<b>CV</b>	<b>Cardiovascular</b>
<b>DBP</b>	<b>Diastolic blood pressure</b>
<b>ECG</b>	<b>Electrocardiogram</b>
<b>HTN</b>	<b>Hypertension</b>
<b>hUAT</b>	<b>human uric acid transporter</b>
<b>IHD</b>	<b>Ischemic heart disease</b>
<b>JNC</b>	<b>Joint national committee</b>
<b>NO</b>	<b>Nitric oxide</b>
<b>OSA</b>	<b>Obstructive sleep apnea</b>

<b>OAT</b>	<b>Organic anion transporter</b>
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**SBP**

**SUA**                      **serum uric acid**

**UA**                      **uric acid**

**URAT**                      **urate transporter**

**WHO** **world health organization**



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## **1.1 Introduction:**

Hypertension (HTN) in adults is the most common form of cardiovascular diseases. The prevalence of hypertension grows higher with aging, resulting in an increase in morbidity and mortality through various events such as myocardial infarction, heart failure, stroke, and renal failure (1-3).

Hypertension is an important, increasing medical and public health problem. Worldwide prevalence estimates for hypertension may be as much as 1 billion individuals and approximately 7.1 million deaths per year may be attributable to hypertension (4). The world health organization( WHO ) reports that suboptimal blood pressure ( $>115$  mm of Hg Systolic BP) is responsible for 62% of cerebrovascular disease and 49% of ischemic heart disease(IHD). In addition, suboptimal blood pressure is the first attributable risk for death due to myocardial infarction, stroke, congestive heart failure, peripheral vascular disease and end stage renal disease throughout the world (4). Approximately 30% of adults are still unaware of their elevated blood pressure, more than 40% of individuals are not on treatment, and two thirds of hypertensive patients are not being controlled to BP levels less than 140/90 mm of Hg (4).

Uric acid, which serves no biochemical function other than being an end product of purine metabolism, was first discovered in 1776. A Swedish chemist Scheele isolated it from a urinary tract stone. In 1797, a British chemist Wallaston detected uric acid in a tophus which was removed from his own ear. About 50 years later Alfred Baring Garrod, a British physician showed by chemical isolation that uric acid was abnormally high in gouty patients. In subsequent studies Garrod formulated a rational relationship between hyperuricemia and symptomatology of gouty patients (4).

Hyperuricemia has been proposed to have an association with hypertension in various studies. Serum uric acid (UA) levels were demonstrated to be an independent predictor for developing hypertension (5,6,7). Regardless of the different ethnic origins, a continuous relationship between serum UA and blood pressure (BP) was observed in African-Americans and whites (8, 9) as well as in Asians (7, 10) including Koreans (11-13). For determining the causal role of serum UA in the development of hypertension, Mazzali et al. (14) demonstrated an elevation in serum UA followed by an increase in BP via a crystal-independent mechanism in rat models. Reduction of serum UA was associated with a decrease in BP through the regulation of renin-angiotensin and nitric oxide system. Therefore, the study aim to evaluate



serum uric acid levels in sudanese hypertensive patients living in khartoum state .

## **1.2 Objectives:**

### **1.2.1 General objective:**

To study the serum uric acid levels in sudanese hypertensive patients living in khartoum state .

### **1.2.2 Specific objectives:**

- To determine the prevalence of hyperuricemia(Gout) in sudanese hypertensive patients.
- To study the association of serum uric acid level to duration and severity of hypertension.

### **1.3 Review of literature:**

#### **1.3.1 Hypertension:**

Hypertension or high blood pressure is a common condition in which the long term force of the blood against the artery wall is high enough that it may eventually cause health problems such as heart disease. Hypertension is the third leading killer disease in the world and is responsible for 1 in every 8 deaths. About 1 billion people are affected by hypertension worldwide . The prevalence of hypertension is known to increase with age. Over 50% of individuals aged 60 to 69 and over 75% of those aged 70 years and older are affected. Recent Framingham Heart Study reported that life time risk of developing hypertension is approximately 90% for men and women who are normotensive at 55-65 years old and survived to the age of 80-85 years (15).

Studies have shown that BP is an independent risk factor for cardiovascular disease(CVD). This relationship is independent, consistent and continuous. Observations involving more than 1 million individuals

have shown that death from both CVD and stroke increases progressively and linearly from BP levels of as low as 115mmHg systolic and 75 mmHg diastolic upwards. The increased risks are present in all age groups ranging from 40 to 89 years old. For every increment of 20 mmHg systolic or 10 mmHg diastolic there was a doubling of mortality from both ischemic heart disease and stroke (16).

Evidence also warrants greater attention to the importance of systolic blood pressure (SBP) as a major risk factor for CVD. The rise in SBP continues throughout life, in contrast to diastolic blood pressure (DBP), which rises until approximately 50 years age, tends to level off over the next decade, and may remain same or fall later in life. Clinical trials have demonstrated that control of isolated systolic hypertension reduces total mortality, cardiovascular (CV ) mortality and stroke (17,18).

Blood pressure is determined both by the amount of blood pump by heart and the amount of resistance to blood flow in arteries. The more blood pumps by the heart, and the narrow arteries, the higher blood pressure. Normally blood pressure is 120 over 80 mmHg, but hypertension is higher than 130 over 80 mmHg.

### **1.3.1.1 Mechanism of hypertension:**

The roles of sodium and potassium in the pathogenesis of hypertension (19) appropriately emphasize the central roles of an excess of sodium, the expansion of extracellular fluid volume, the release of digitalis-like factor, a potassium deficit, and  $\text{Na}^+/\text{K}^+$ -ATPase inhibition. Digitalis-like factor is found mainly in the low renin, volume-expanded types of hypertension. A few clinical observations suggest that, in contrast to the effect of sodium chloride, blood pressure is not increased when sodium is consumed in the absence of chloride. In stroke prone, spontaneously hypertensive rats, the rate of increase of blood pressure over time is specifically related to the chloride content of the diet. It seems appropriate to acknowledge the potential importance of the chloride ion in the pathogenesis of sodium-sensitive hypertension. However, from a clinical perspective, since most dietary sodium is ingested in the form of sodium chloride, it may be more practical to relate dietary recommendations specifically to sodium. Digitalis-like factor mediates sodium retention by increasing the activity and expression of the renal sodium pump. However, most studies have shown that ouabain and other digitalis-like steroids specifically inhibit the activity of the  $\text{Na}^+/\text{K}^+$ -ATPase sodium pump in all cells tested (19).

### **1.3.1.2 Pathologic consequences of hypertension:**

Many pathophysiologic factors have been implicated in the genesis of essential hypertension, increased sympathetic nervous system activity, perhaps related to heightened exposure or response to psychosocial stress; overproduction of sodium-retaining hormones and vasoconstrictors; long-term high sodium intake; inadequate dietary intake of potassium and calcium; increased or inappropriate renin secretion with resultant increased production of angiotensin II and aldosterone; deficiencies of vasodilators, such as prostacyclin, nitric oxide (NO), and the natriuretic peptides; alterations in expression of the kallikrein-kinin system that affect vascular tone and renal salt handling; abnormalities of resistance vessels, including selective lesions in the renal microvasculature; diabetes mellitus; insulin resistance; obesity; increased activity of vascular growth factors; alterations in adrenergic receptors that influence heart rate, inotropic properties of the heart, and vascular tone; and altered cellular ion transport. The structural and functional abnormalities in the vasculature, including endothelial dysfunction, increased oxidative stress, vascular remodeling, and decreased compliance, may antedate hypertension and contribute to its pathogenesis has gained support in recent years.

Although several factors clearly contribute to the pathogenesis and maintenance of blood pressure elevation, renal mechanisms probably play

a primary role, other mechanisms amplify (for example, sympathetic nervous system activity and vascular remodeling) or buffer (for example, increased natriuretic peptide or kallikrein–kinin expression) the pressor effects of renal salt and water retention. These interacting pathways play major roles in both increasing blood pressure and mediating related target organ damage (20).

### **1.3.1.3 Classification of blood pressure:**

Based on the seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure (JNC VII report) BP is classified into the following stages.

**Table: (1.1) classification of BP according to JNC VII Report:**

Classification of BP	Systolic BP (mmHg)	Diastolic BP (mmHg)
Normal	< 120	<80
Prehypertension	120 - 139	80 - 89
Stage 1 hypertension	140 - 159	90 - 99
Stage 2 hypertension	≥160	≥100

In contrast with the classification provided in the JNC VI report, a new category designated prehypertension has been added and stages 2 and 3 have been combined (20).

Patients with arterial hypertension and no definable cause are said to have Primary or essential or idiopathic hypertension. Individuals in whom a specific structural organ or gene defect is responsible for hypertension are defined as having a secondary form of hypertension (21).

- Primary (essential) hypertension: For most adult; there is no identifiable cause of high blood pressure. This is type of high blood pressure called primary (essential) hypertension tend to develop gradually over many years.
- Secondary hypertension: High blood pressure caused by underlying condition. This is type of high blood pressure called secondary hypertension tend to appear suddenly and cause higher blood pressure than does primary hypertension.

Various conditions lead to secondary hypertension: Obstructive sleep apnea, Kidney problems, Adrenal gland tumor, Thyroids problems, Medications such as contraceptive pills, cocaine and amphetamines.

#### **1.3.1.4 Accurate blood pressure measurement:**

Three sitting BP measurements at a 1 minute interval must performed according to current guidelines (cuff adjustment for arm's circumference) using an certified manual BP measuring device (22).

### **1.3.1.5 Hypertension genetic considerations:**

Twin studies document greater concordance of blood pressures in monozygotic than dizygotic twins, and population studies show greater similarity in blood pressure within families than between families. Adoption studies demonstrate greater concordance of blood pressure among biological siblings than adoptive siblings living in the same household. Furthermore, single genes can have major effects on blood pressure, accounting for the rare Mendelian forms of high and low blood pressure. Mutations in 10 genes that cause Mendelian forms of human hypertension and 9 genes that cause hypotension have been described to date, as reviewed by Lifton and his colleagues. These mutations affect blood pressure by altering renal salt handling that the development of hypertension depends on genetically determined renal dysfunction with resultant salt and water retention. In most cases, hypertension results from a complex interaction of genetic, environmental, and demographic factors. Improved techniques of genetic analysis, especially genome-wide linkage analysis, have enabled a search for genes that contribute to the development of primary hypertension in the population. Application of these techniques has found statistically significant linkage of blood pressure to several chromosomal regions; including regions linked to familial combined hyperlipidemia. These findings suggest that there are



many genetic loci, each with small effects on blood pressure in the general population. Overall, however, identifiable single gene causes of hypertension are uncommon, consistent with a multifactorial cause of primary hypertension. The candidate gene approach typically compares the prevalence of hypertension or the level of blood pressure among individuals of contrasting genotypes at candidate loci in pathways known to be involved in blood pressure regulation. The most promising findings of such studies related to genes of the renin–angiotensin–aldosterone system, such as the *M235T* variant in the angiotensinogen gene, which has been associated with increased circulating angiotensinogen levels and blood pressure in many distinct populations, and a common variant in the angiotensin-converting enzyme (ACE) gene that has been associated in some studies with blood pressure variation in men. The best studied monogenic cause of hypertension is the Liddle syndrome, a rare but clinically important disorder in which constitutive activation of the epithelial sodium channel predisposes to severe, treatment-resistant hypertension. Epithelial sodium channel activation has been traced to mutations in the subunits of the channel, resulting in inappropriate sodium retention at the renal collecting duct level. Patients with the Liddle syndrome typically present with volume-dependent, low renin, and low-aldosterone hypertension. Screenings of general hypertensive populations indicate that the Liddle syndrome is rare and does not contribute

substantially to the development of hypertension in the general population (23).

#### **1.3.1.6 Hypertension symptoms and signs:**

Most people with high blood pressure have no sign or symptom even if blood pressure readings reach dangerously high level. A few people with high blood pressure may have headache, shortness of breath, but these signs and symptoms are not specific and usually do not occur until high blood pressure has reached severe or life threatening stage.

#### **1.3.2 Association of hypertension with other conditions:**

##### **1.3.2.1 Obesity:**

Hypertension is more common among obese individuals and adds to their increased risk of (IHD) especially if it is abdominal/visceral in location as a part of the metabolic syndrome. In the Framingham Study the incidence of hypertension was increased 46 % in men and 75 % in female who are overweight defined as a body mass index of 25.0 to 29.9 compared to normal weight persons (24).

##### **1.3.2.2 Physical Inactivity:**

People who are inactive tend to have higher heart rate. The higher heart rate, the harder heart must work with each contraction and the stronger the

force on arteries. Lack of physical activity also increases the risk of being over-weight (25).

#### **1.3.2.3 Alcohol Intake:**

Light to moderate alcohol consumption can decrease the risk of hypertension, whereas heavy alcohol intake is associated with an increased risk of hypertension. The association between alcohol consumption and hypertension may be changed by age (26).

#### **1.3.2.4 Smoking:**

A large number of observations identify cigarette smoke as a factor able to cause a functional and initially transient damage primarily of the endothelium and reduced tolerance to exercise stress testing because of the effects of nicotine and carbon monoxide. At the time, the functional damage became an irreversible pathological damage with ischemic lesions of the myocardium and artery vessel atherosclerosis. In its turn, hypertension plays harmful effects on the heart, kidney and arterial tree, mainly coronary, carotid and cerebral vascular structures, by its complications, the target organs of which are the same of cigarette smoke (27).

#### **1.3.2.5 Sleep Apnea:**

Obstructive sleep apnea (OSA) is related to an increased risk of resistant hypertension. Mild, moderate and severe OSA is associated with essential hypertension; as well a dose-response manner relationship is manifested. The associations are relatively stronger among Caucasians and male OSA patients (24).

#### **1.3.2.6 Hypercholesterolemia:**

Hyperlipidemia is twice as common in hypertensives in Africa compared to the general African population. Genderwise, hyperlipidemia was commoner among Hypertensives that are female (25).

#### **1.3.2.7 Hyperuricemia:**

The long-term effects of hypertension are well-known and in India is especially vulnerable to its impact. Since serum uric acid levels are strongly correlated with hypertension, evaluation of serum uric acid levels in patients at risk for hypertension and in those suffering from hypertension should be done as early as possible in the course of the disease. Treatment of hyperuricemia in hypertension with appropriate therapy may thus be a valuable addition to its management (28).

### **1.3.3 Uric acid metabolism:**

Uric acid is a heterocyclic compound of carbon, nitrogen, oxygen and hydrogen with formula  $C_5H_4N_4O_3$ . Uric acid is the final breakdown product of purine degradation in humans. Urates, the ionized forms of uric acid, predominate in plasma extracellular fluid and synovial fluid, with 98% existing as monosodium urate at pH 7.4 (29).

The pH of urine greatly influences the solubility of uric acid. Although purine nucleotides are synthesized and degraded in all tissues, urate is produced only in tissues that contain xanthine oxidase, primarily in the liver and small intestine. Urate production varies with the purine content of the diet and the rates of purine biosynthesis, degradation, and salvage. Normally, two-third to three-fourth of urate is excreted by the kidney, and most of the remainder is eliminated through the intestine. The kidneys clear urate from the plasma and maintain physiologic balance by utilizing specific organic anion transporters (OATs) including urate transporter 1 (URAT1) and human uric acid transporter (hUAT). URAT1 and other OATs carry urate into the tubular cells from the apical side of the lumen. Once inside the cell, urate must pass to the basolateral side of the lumen in a process controlled by the voltage-dependent carrier hUAT. Until recently, component model has been used to describe the renal handling of urate / uric acid.

URAT1 is a novel transporter expressed at the apical brush border of the proximal nephron. Uric acid compounds directly inhibit URAT1 on the apical side of the tubular cell (so-called cis-inhibition) (30).

### **1.3.3.1 Hyperuricemia:**

The normal range for serum uric acid( SUA) levels was 2.40–5.70mg/dl in females and 3.40–7.00mg/dl in males respectively. Values above the upper limit were considered as hyperuricemia (31).

### **1.3.3.2 Causes of Hyperuricemia:**

Hyperuricemia may be classified as *primary* or *secondary* depending on whether the cause is innate or is the result of an acquired disorder. However it is useful to classify hyperuricemia in relation to the underlying pathophysiology, i.e., whether it results from increased urate production, decreased excretion, or a combination of two.

\_Urate over production can be caused by idiopathic factor (primary), HPRT deficiency, PRPP synthetase overactivity, Hemolytic process, Lymphoproliferative diseases, Myeloproliferative diseases, Polycythemia vera, Psoriasis, Paget's disease, Glycogenosis III, V, and VII, Rhabdomyolysis, Alcohol, Obesity.

\_ Decreased Uric acid Excretion is either to be caused by Primary idiopathic, . Renal insufficiency, Polycystic kidney disease, Diabetic insipidus, Hypertension, Acidosis.

#### **1.3.3.3 Classification of Hyperuricemia by Pathophysiology:**

Hyperuricemia can be classified into two types:

(a) Primary or idiopathic hyperuricemia:

The hyperuricemia is considered primary when it exists in the absence of coexisting diseases or drugs that alter uric acid production or excretion. It usually last lifelong.

(b) Secondary hyperuricemia:

This refers to excessive urate production (overproducer) or diminished renal clearance (under excretory) occurring as a consequence of another disease, drug and dietary product or toxin (32).

#### **1.3.3.4 Complications of hyperuricaemia:**

Cardiovascular disease:

Hyperuricemia may increase risk factors for cardiovascular disease (33).

Type 2 diabetes:

Hyperuricemia may be a consequence of insulin resistance in diabetes rather than in precursor. One study showed high serum uric acid was associated with higher risk of type 2 diabetes, independent of obesity, dyslipidemia and hypertension. Hyperuricemia is associated with components of metabolic syndrome, including in children.

#### **1.3.3.4.1 Uric acid stone formation:**

Kidneys stones can form through deposits of sodium urate microcrystals. Saturation levels of uric acid in blood may result in one form of kidney stones when the urate crystallizes in the kidney. These uric acid stones are radiolucent and so do not appear on an abdominal plain x-ray. Uric acid crystals can also promote the formation of calcium oxalate stones and acting as seed crystals.

#### **1.3.3.4.2 Gout:**

The most recognized complication of hyperuricemia is *gouty arthritis*. In the general population the prevalence of hyperuricemia ranges between 2.0 and 13.2% and the prevalence of gout is between 1.3 and 3.7%. The higher the serum urate level, the more likely an individual is to develop gout. In one study, the incidence of gout was 4.9% for individuals with serum urate concentrations >540  $\mu\text{mol/l}$  (9.0 mg/dl) compared with 0.5% for those with values between 415 and 535  $\mu\text{mol/l}$  (7.0 and 8.9mg/dl).



The complications of gout correlate with both the duration and severity of hyperuricemia (34)..

#### **1.3.3.4.3 Hyperuricaemia and Renal System:**

Hyperuricemia also causes several renal problems: Nephrolithiasis, Urate nephropathy, a rare cause of renal insufficiency attributed to monosodium urate crystal deposition in the renal interstitium and Uric acid nephropathy, a reversible cause of acute renal failure resulting from deposition of large amounts of uric acid crystals in the renal collecting ducts, pelvis, and ureters (35).

#### **1.3.4 History of uric acid and hypertension:**

Hyperuricemia leads to the increase in BP values by stimulating oxidative stress and inflammatory mechanisms through endothelial dysfunction and proliferation of smooth muscle cells in the blood vessels and stimulation of the renin-angiotensin system (36).

## **2. MATERIALS AND METHODS**

### **2.1 Study design:**

A case – control study

### **2.2 Period of study:**

March to July 2019

203 Study area:

Khartoum state capital of sudan, Alhuda private clinic.

#### **2.4 Study Population:**

54 hypertensive patients aged between 20-80 years were participated in this study from Khartoum state capital of sudan.

54 normotensive healthy adults age between 20-80 years were served as control.

#### **2.5 Inclusion Criteria:**

- Age group between 20 to 80 years.
- Both sexes were included.
- Stage 1 and stage 2 Hypertension according to JNC-VII.

#### **2.6 Exclusion Criteria:**

- Hypertensive patients with target end organ damage
  - a) Hypertensive Heart disease as evidenced by Left Ventricular hypertrophy on electrocardiogram (ECG) voltage criteria / Hypertensive crisis / Malignant Hypertension.
  - b) Hypertensive Nephropathy
  - c) Hypertensive Retinopathy
- Diabetes Mellitus – Type 1 and Type 2 or metabolic syndrome.
- Patients with Chronic kidney disease.
- Hypertensive Patients with known Cerebro-vascular disease.

- Hypertensive Patients with coronary Artery disease – Myocardial Ischemia or Infarction.
- Patients with long term drug intake like steroids, Anti-Tuberculous Treatment (ATT), diuretics, antimetabolite or chemotherapy drugs.

## **2.7 Sample size:**

A convenience sample of 108; 54 control and 54 cases

## **2.8 Ethical consideration:**

The study was approved by the Ethical Committee of Faculty of Medicine, International University of Africa.

## **2.9 Written formal Consent:**

The study groups identified by the above criteria (inclusion and exclusion) were first informed about the nature of the study. Participants willing for the study were selected after getting an informed and written consent from them.

Thus, a total of 54 patients was taken up for study that satisfied the inclusion and exclusion criteria. Similarly, 54 age and sex matched subjects was kept as control.

## **2.10 Data collection:**

Data was collected from participants using an anonymous standardized research tool (annex 1). Socio-demographic data was collected and

include age, gender, ethnic group, and toxic habits such as smoking, tobacco and alcohol consumption.

### **2.11 Blood pressure measurement method:**

Blood pressure was measured by using a mercury sphygmomanometer, properly sized blood cuff was wrap around the; and one inch above the antecubital fossa, the stethoscope's bell lightly pressed over the brachial artery just below the cuff's edge. the cuff was inflated rapidly to 180 mmHg , the air released from the cuff at moderate rate; and observed sphygmomanometer while listening with stethoscope , the first knocking sound is the systolic pressure ,when the knocking disappears that is the diastolic blood pressure.

### **2.12 Anthropometric measurements:**

#### **2.12.1 Weight and height methods:**

Calibrated weight and height measure scale was used for weight measurement. Firstly the person was asked to remove any heavy clothes or items; then person's feet were set onto center of the scale platform with feet slightly a part for better balance, and ask person to look straight and then record the weight. For height measurement; the person was asked to remove his/her shoes prior to taking measurement; person was be stand with his-her feet slightly a part and back as straight as possible with the heels, shoulders should touch the surface of height board. Person

was asked to look straight ahead with head erect, the headpiece was placed flat against the wall at a right angle to the head, the headpiece was lowered until it firmly touches the crown of the head and the measurement was recorded.

### **2.1202 BMI:**

Body mass index (BMI) was calculated as weight kg/height squared ( $\text{kg/m}^2$ ) and subjects were considered as normal weight if their BMI was  $< 25 \text{ kg/m}^2$ , overweight if their BMI from 25 to  $29 \text{ kg/m}^2$  and obese if their BMI  $\geq 30 \text{ kg/m}^2$ .  $\text{BMI} = \text{Wt}/\text{H}^2 \text{ kg/m}^2$ .

### **2.13 Sample collection:**

Five ml of venous blood was drawn from antecubital vein of patients in a plain vacutainer tube under sterile conditions after fulfilling the selection criteria. Serum separated by centrifugation at 3000 rpm for 15 minutes and the separated serum stored at  $-200^\circ\text{C}$  for uric acid analysis.

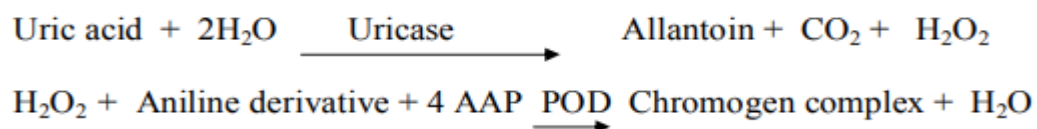
### **2.14 Uric acid measurement:**

Method: URICASE/POD, End point assay

Principle:

Uric acid is oxidized to Allantoin and hydrogen peroxide by the enzyme uricase. In the presence of peroxidase, released hydrogen peroxide is

coupled with aniline derivative and 4-amino antipyrine to form colored chromogen complex. Absorbance of colored dye is measured at 550nm and is proportional to the concentration of uric acid in the sample.



**Reagents: Table (2.1)**

S.NO	REAGENT	COMPOSITION
1.	Uric acid mono Reagent	Triss buffer(pH 8.25) Uricase TBHB 4-Aminoantipyrine Peroxidase
2.	Uric acid standard	Uric acid Stabilizer Preservative

Reagent storage and stability: Reagents are stable at 2-80 C

**Sample: Table (2.2)**

<b>SERUM</b>	<b>Storage at</b>	<b>Stability</b>
	Room temperature(15-30 <sup>0</sup> C)	3 Days
	2-8 <sup>0</sup> C	7 Days
	-20 <sup>0</sup> C	6 Months

Assay Parameters:

Mode ----- End Point

Wave Length ---- 550 nm

Flow Cell temperature ---- 37°C

Optical path length ----- 1 cm

Blanking ----- Reagent Blank

Sample Volume ----- 20 µl

Reagent Volume ---- 1000 µl

Incubation time -----5 min

Concentration of standard ----- 6mg/dl

Stability of final colour ----- 15 min

Permissible Reagent Blank Absorbance ----- <0.4AU

Linearity ----- 25mg/dl

Units ----- mg/dl

**Procedure: Table (2.3)**

	<b>Blank</b>	<b>Standard</b>	<b>Test</b>
Serum	-	-	20 µl
Reagent 2	-	20 µl	-
Reagent 1	1000µl	1000 µl	1000 µl

Mixed well. Incubated at 37°C for 5 minutes.

The analyzer was programmed as per assay parameters.

1. The analyzer was blanked with reagent blank.
2. Absorbance of standard followed by the test is measured.
3. Results were calculated as per given calculation formula

**2.14 Statistical analysis:**

The Data was computerized through free downloadable software developed by the Centre of Disease Control, CDC/Atlanta, USA: Epi-info



7TM 7.5.1.2. The statistical packages for social sciences (SPSS version 23) were used to clean, describe and analyse the data. Descriptive statistics to summarize count data graphically (frequency tables for estimation of prevalence and graphics) and numerically for continuous variables (mean, standard deviation, median). Statistical analysis was used ANOVA and t test to establish the relationship between hypertension and uric acid levels. All tests were considered as statistically significant when  $p\text{-value} < 0.05$ .

### 3. Results

During the study period from march 2019 to July 2019 a total of 108 participants were studied of which 54 patients were cases and 54 were controls who were participants without hypertension or any other condition known to cause raised serum uric acid levels.

301 Age distribution of participants:

Among the studied population, 78 participants fell in the age groups between 30 – 49 years of age. Only 30 of participants fell in the extreme ages of studied population. All the age groups in both cases and controls were matched well with subtle variations. Table (3.1) and Fig 1.

Table (3.1) Age distribution of participants (N=108)

Age groups	Cases	controls	Total
30 – 39	14	21	35
40 – 49	24	19	43
50 – 59	14	11	25
60 – 69	2	3	5
Total	54	54	108

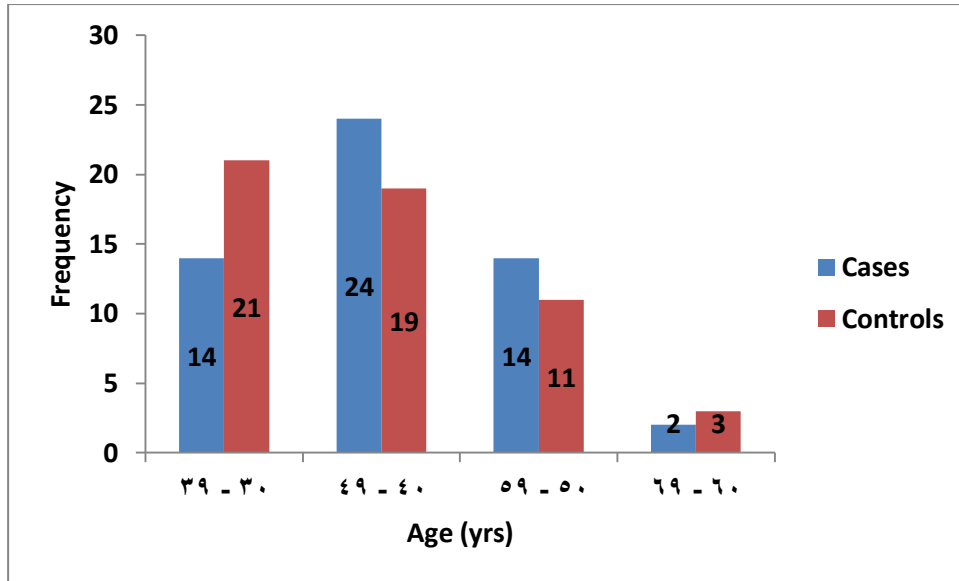


Figure (3.1). Age distribution of participants

### 3.2 Gender distribution:

Among the cases, total number of male patients was 37 and total number of female patients was 17. Among the controls, total number of male patients was 36 and total number of female patients was 18. Table (3.2), Fig 2.

Table (3.2) Gender distribution of participants

Gender	Male	Female
Cases	37	17
Controls	36	18
Total	73	35

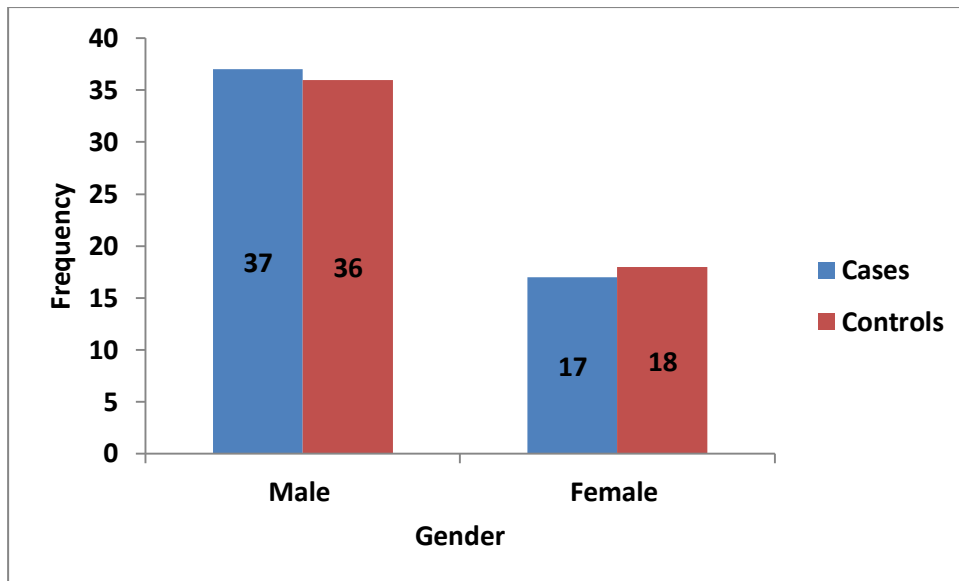


Figure (3.2). Gender distribution of participants

### 3.3 Clinical characteristics of control participants:

Table (3.3) shows the clinic characteristics of control participants. The mean of pulse rate was  $72.8 \pm 2.88$  and mean of systolic blood pressure was  $125 \pm 1.99$ , mean of diastolic blood pressure was  $80 \pm 2.91$ , mean of respiratory rate was  $18 \pm 2.32$ .

Table (3.3) clinical characteristics of control participants

	N	Minimum	maximum	Mean	Std. Deviation
<b>Pulse rate</b>	54	68	79	72.8	2.88
<b>Systolic BP</b>	54	120	130	125	1.99
<b>Diastolic BP</b>	54	70	90	80	2.91
<b>Respiratory rate</b>	54	15	23	18.18	2.32
<b>Temperature</b>	54	36	38	36.43	0.72
<b>Uric acid levels</b>	54	3.7	6.00	4.48	0.54

### 3.4 Clinical characteristics of case participants:

Table (3.4) shows clinic characteristics of case participants. The mean of pulse rate was  $74 \pm 2.33$ , the mean of systolic blood pressure was  $153 \pm 5.52$ , the mean of diastolic blood pressure was  $90 \pm 4.45$  and the mean of respiratory rate was  $18.77 \pm 3.21$ .

Table (3.4) clinical characteristics of case participants

	N	Minimum	maximum	Mean	Std. Deviation
<b>Pulse rate</b>	54	67	80	74.66	2.33
<b>Systolic BP</b>	54	120	180	153	5.52
<b>Diastolic BP</b>	54	80	99	90	4.45
<b>Respiratory rate</b>	54	13	32	18.77	3.21
<b>Temperature</b>	54	36	38.5	36.64	0.55
<b>Uric acid levels</b>	54	5.8	7.9	7.6	0.37

### 3.5 Distribution of BMI for case participants:

The results demonstrated that 9.3% of case participants were underweight, 16.7% were normal weight, 25.9 were overweight and 48.1% were obese class I. table (4) fig 3.

Table (3.5) Distribution of BMI for case participants

BMI categories	Frequency	Percent (%)
<b>Under weight</b>	5	9.3
<b>Normal weight</b>	9	16.7
<b>Over weight</b>	14	25.9
<b>Obese I</b>	26	48.1

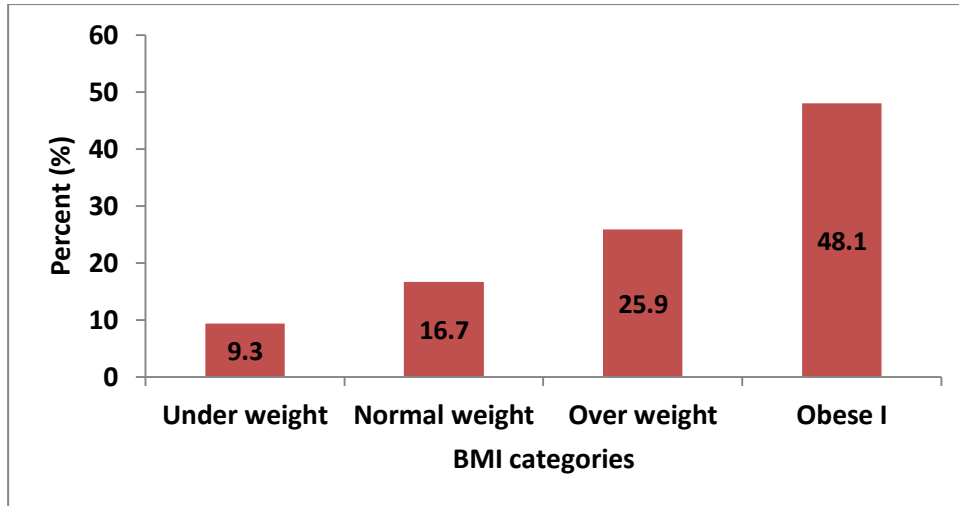


Figure (3.3). Distribution of BMI for case participants

### 3.6 History, clinical manifestations and habit:

Table (3.6) shows history of post-diabetes mellitus and post-stroke in case participants and also shows family history of diabetes mellitus and stroke in case participants. In addition, table (3.6) shows clinical manifestation and habit of case participants.

Table (3.6) History, clinical manifestation and habit

Characteristics	Frequency	Percent (%)
Post diabetes mellitus	6	11.1
Post stroke	1	1.9
Family history of diabetes mellitus	43	79.6
Family history of stroke	24	44.4
Pallor	9	16.7
Clubbing	3	5.6
Edema	18	33.3
Xanthoma	4	7.4
Tophi	10	18.5
Arthritis	20	37
Rhythm (abnormal)	3	5.7
Character (abnormal)	18	33.9
Vessel wall condition	35	64.8
vegetable	13	24.5
Non-vegetable	41	75.5
Tobacco (snuff)	11	20.8
Smoking	12	22.6

### 3.7 Duration of HTN Patients in case group:

The duration of hypertension in case group was divided into three categories hypertensive those for duration of hypertension < 10, duration of hypertension 10 - 20 and duration of hypertension 21 - 31 years. The total number of patients with hypertension for duration of < 10 years was 14 cases, the total number of cases with duration of hypertension 10 – 20 years was 28 cases and the total number of cases with duration of hypertension 20 – 31 years was 12 cases. Figure 4.

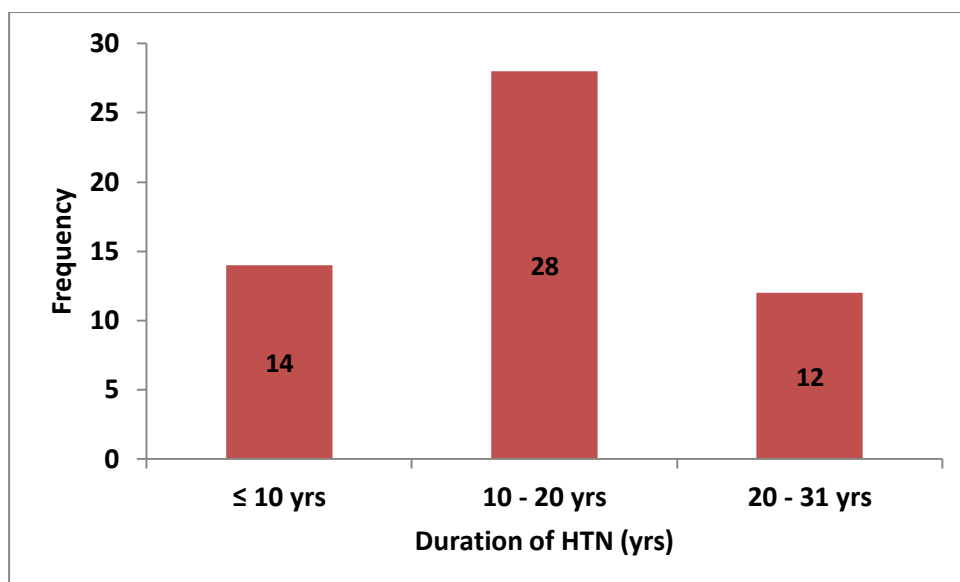


Figure (3.4). Duration of hypertension in case group

### 3.8 Uric acid levels among age groups in case participants:

The comparison of serum UA levels of hypertensive subjects in different age groups are presented in Figure( 305) Serum UA levels were significantly higher in subjects with hypertension among all the age groups(mean 7.6) compared to normotensive subjects(mean 4.4)0. Serum

uric acid levels were significantly higher in non-elderly subjects (< 50 yrs) compared with elderly subjects (> 50 yrs) ( $P > 0.05$ ).

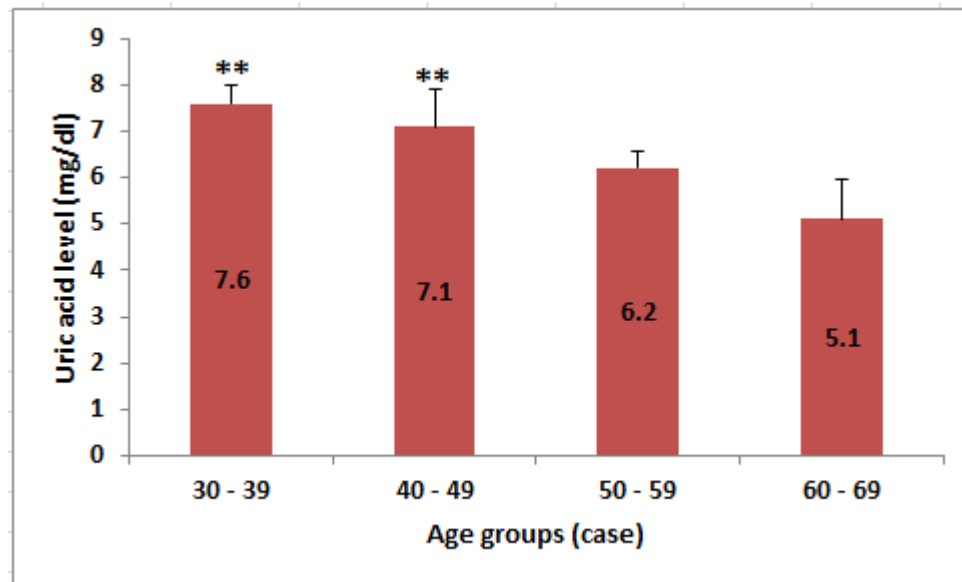


Figure (3.5). Uric acid levels among age groups in case participants

### 3.9 Uric acid levels among BMI categories in case group:

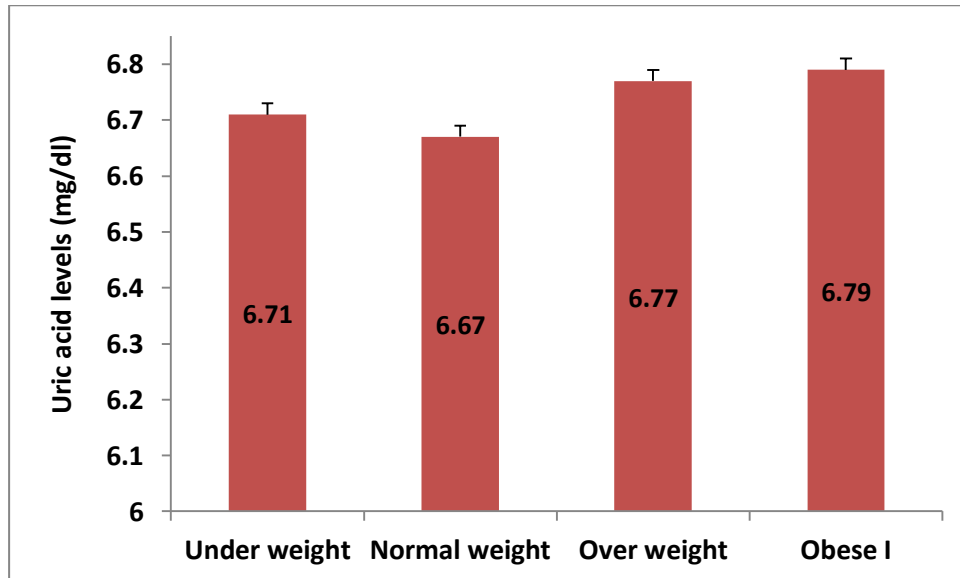
The mean of uric acid level in underweight cases was  $6.71 \pm 0.11$  mg/dl.

The mean of uric acid level in normal weight cases was  $6.67 \pm 0.71$  mg/dl. The mean of uric acid level in overweight cases was  $6.77 \pm 0.57$  mg/dl. The mean of uric acid level in obese cases was  $6.79 \pm 0.28$  mg/dl.

The data analysis showed that there was no significant difference in the level of uric acid in BMI categories. Figure (3.6).



Figure (3.6).



### 3.10 Comparison of components of blood pressure between case and control:

The present study showed that the mean of systolic blood pressure among cases was  $153 \pm 13.5$  mmHg and mean of diastolic blood pressure among cases was  $90 \pm 12.2$  mmHg.

Mean of systolic blood pressure among control was  $126 \pm 11.3$  mmHg and mean of diastolic blood pressure among control was  $80 \pm 9.3$  mmHg.

There was significant rise in the components of blood pressure in case group when compared with control group  $P < 0.003$ . Figure (3.7).

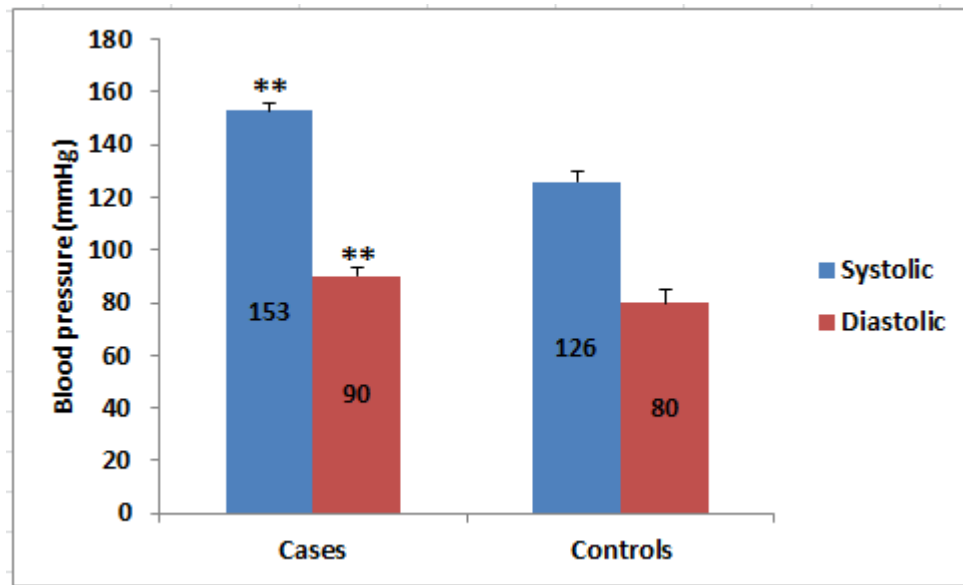


Figure (3.7). Blood pressure components in case and control groups. \*\*P < 0.003 vs. control group.

### 3.11 Uric acid levels in case and control groups:

The total numbers of cases were 54 (both male and female), the data analysis of the cases showed the mean uric acid level to be  $7.6 \pm 0.37$  mg/dl.

The total numbers of controls were 54 (both male and female), the data analyzed showed a mean uric acid to be  $4.48 \pm 0.54$  mg/dl. Our results demonstrated that there was significant rise in uric acid level in case group when compared with control group P < 0.001. figure (3.8)

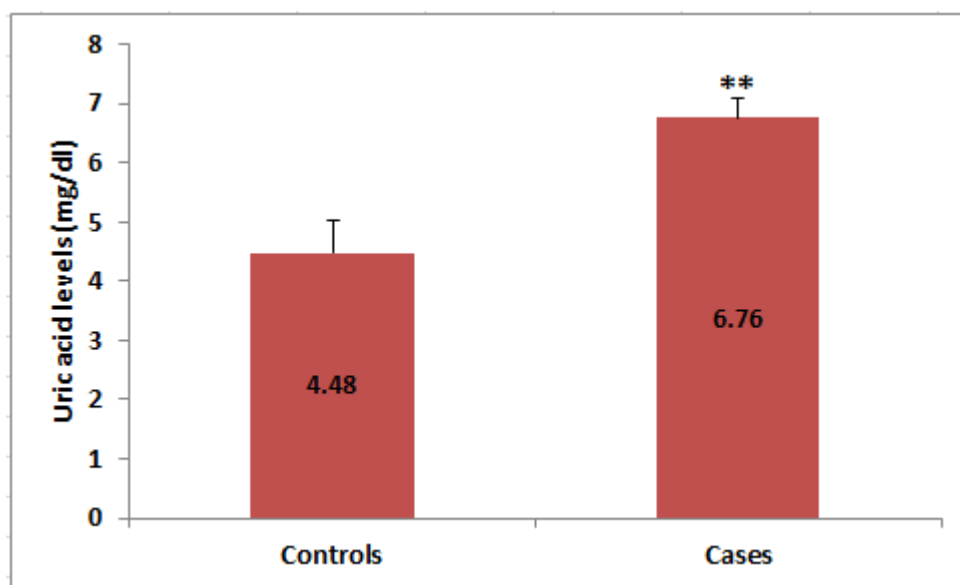


Figure (3.8). Uric acid levels in case and control groups. \*\*P < 0.001 vs. control group.

### 3.12 Number of cigarette per day in case group:

The number of cigarette per day in case group was divided into four categories; 3 cigarettes per day, 4 cigarettes per day, 5 cigarettes per day and more than 6 cigarettes per day. The total number of patients take 3 cigarettes per day was 4, take 4 cigarettes per day was 3 and these who take more than 5 cigarettes per day was 5 patients. Figure (3.9).

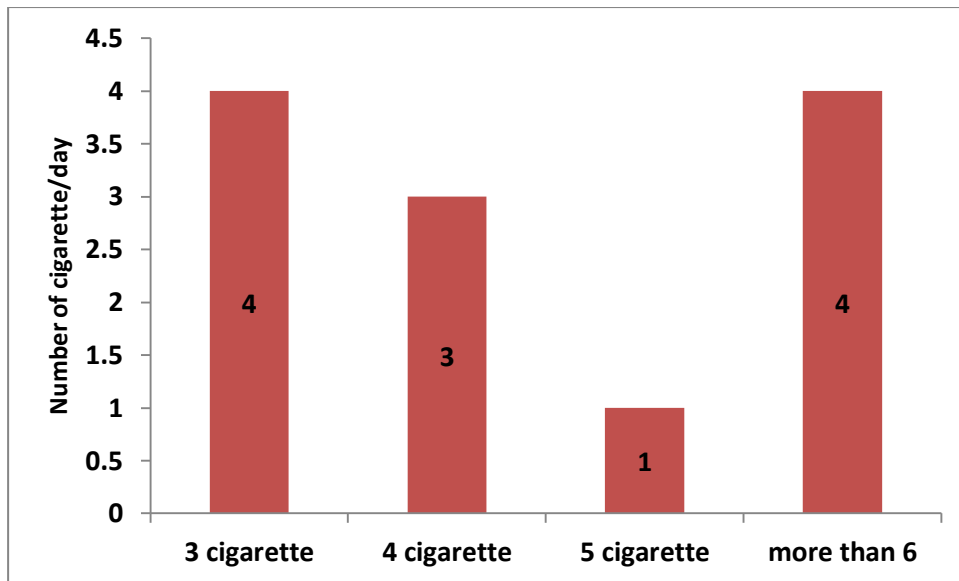


Figure (3.9). Number of cigarette per day in case group.

### 3.13 Smoking duration in case group :

The smoking duration in case group was divided into two categories; less than 15 years and more than 15 years. The total number of patients with duration of smoking less than 15 years was 4 and the total number of patients with smoking duration more than 15 years was 8. Figure (3.10).

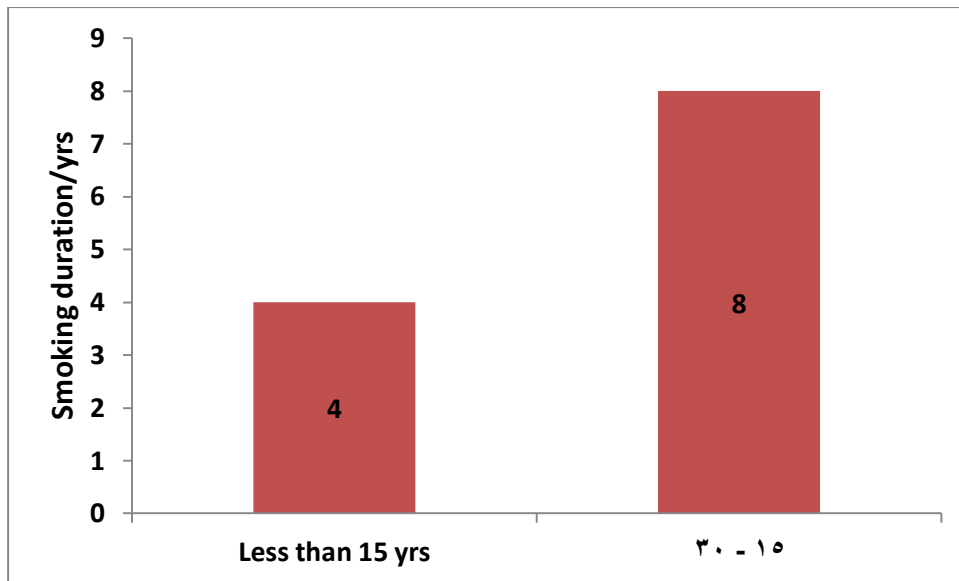


Figure (3.10). Smoking duration in case group.

### 3.14 HTN duration and uric acid levels:

The results showed that the mean of uric acid levels in patients with duration of HTN less than 10 years was  $6.4 \pm 0.32$ , the mean of uric acid levels in patients with duration of HTN 10 – 20 years was  $6.9 \pm 0.79$  and the mean of uric acid levels in patients with duration of HTN more than 20 years was  $7.1 \pm 0.63$ . there was significant decreased in the uric acid levels in patients with duration of HTN less than 10 years when compared to other durations  $P < 0.031$ . figure (3.11).

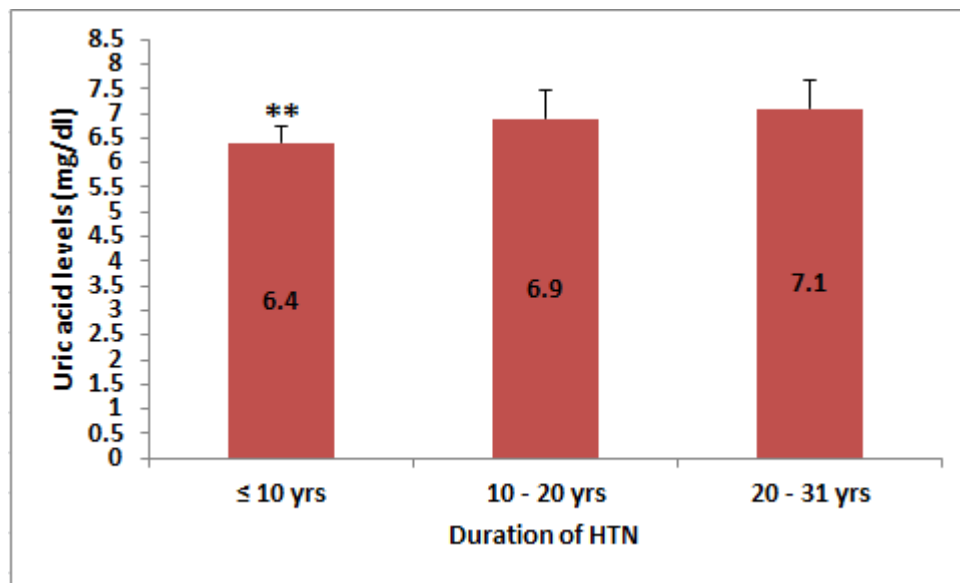


Figure (3.11). HTN duration and uric acid levels. \*\*P < 0.031 vs. 10 – 20 years and 20 – 31 years.

### 3.15 Correlation between components of blood pressure and uric acid levels:

The data analysis demonstrated that there was significant positive correlation between uric acid levels and systolic blood pressure as well as diastolic blood pressure Sig. (2-tailed 0.000). table (3.7).

		Systolic BP	Diastolic BP	Uric acid
<b>Systolic BP</b>	Pearson correlation	1	.711**	.748**
	Sig. (2-tailed)		.000	.000
	N	54	54	54
<b>Diastolic BP</b>	Pearson correlation	.711**	1	.695**
	Sig. (2-tailed)	.000		.000
	N	54	54	54
<b>Uric acid</b>	Pearson correlation	.748**	.695**	1
	Sig. (2-tailed)	.000	.000	
	N	54	54	54

**\*\*.** Correlation is significant at the 0.01 level (2-tailed).

#### **4. Discussion:**

The aim of the present study was to evaluate the relationship between serum uric acid level and hypertension. This study demonstrated that there was significant association between uric acid level with both components of blood pressure systolic and diastolic. Furthermore, The data showed that the serum uric acid levels were significantly higher in non-elderly subjects (< 50 yrs) compared with elderly subjects (> 50 yrs) in hypertensive case. In addition, The result documented that there was significant association between uric acid level and duration of HTN. There was no significant difference in level of uric acid in BMI categories in case participants.

Although serum UA and BP showed a significant relation in the overall population, when we evaluated it according to different age groups (<40, 40–59, ≥60), it was only significant in the non-elderly population under age 60 in both genders. There have been several studies suggesting that the strength of the relationship between serum UA and BP is more dominant in the younger age groups and decreases during the aging process as the duration of hypertension gets longer (1,5,11,,37). However, none of the previous studies have tried to investigate the effect of different age groups on the relation as a primary goal, This study is the

first study to confirm the effect of different age groups on the relation between serum UA and BP.

The prognostic significance of serum UA in different disease entities such as diabetes, chronic kidney disease, and cardiovascular diseases have been recognized in several previous studies (4,8,,38). Understanding the relationship between each diseases and serum UA has been important due to the potential benefit which could be achieved by applying it to new treatment strategies. Feig et al. (22) mentioned that early hypertension developed in children and adolescents with hyperuricemia could be reversed with urate reduction. Considering the practical implications in every day clinical practice, The results suggest the same could be applied beyond the adolescent to the non-elderly adults under age 50 years with early hypertension and hyperuricemia.

In the Current study, we found, a higher level of SUA among hypertensive patients compared with normotensive subjects; SUA levels were associated with the risk of hypertension. Furthermore, The result demonstrated that there was significant decreased in the uric acid levels in patients with duration of HTN less than 10 years when compared to other durations. This findings were consistent with other studies which reported that higher UA concentrations were independently associated with increased period of developing hypertension (39). Potential



mechanisms behind the link between hyperuricemia and the development of hypertension have included nitric oxide and renin-angiotensin aldosterone system pathways. UA could lead to endothelial cell dysfunction via nitric oxide synthetase and stimulate vascular smooth muscle cell proliferation (40). Furthermore, UA may also directly stimulate the renin-angiotensin aldosterone system (14).

The data analysis showed that there was no significant difference in the level of uric acid in BMI categories. In contrast to this results ; Ying Duan et al. (41).demonstrated that a positive significant association between serum uric acid and obesity, especially in high serum uric acid level in overweight and obesity group. Similar result could be found in different studies (42,43) and the association was stronger in females than males in both overweight and obesity group.

There are some limitations to this study. First, the data case-control, and, therefore, it is not possible to establish that relatively higher uric acid levels preceded or caused elevated blood pressure. Second, the sample size of this study was relatively small; therefore, the findings may not represent for the whole sudanese population. Finally, we did not have individual information on family history of hypertension and physical activity which may affect the incidence of high blood pressure.

## **5.1 Conclusion:**

In conclusion, This study demonstrated that there was significant association between uric acid level with both components of blood pressure systolic and diastolic. Furthermore, the data showed that the serum uric acid levels were significantly higher in non-elderly subjects (< 50 yrs) compared with elderly subjects (> 50 yrs) in hypertensive case. In addition, the results documented that there was significant association between uric acid level and duration of HTN.

## **5.2 Recommendations:**

- 1/ Screening for uric acid levels should be part of HTN workup investigations, for hypertensive and cardiovascular patients.
- 2/ Exercise and BMI should be moderators.
- 3/ Study the uric acid level and oxidative stress biomarkers in obese subjects.
- 4/ Screening for the NO and endothelin level in hypertensive patients.

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## Annex (1)

### Questionnaire

**Name :**.....

**Age :**.....

**Sex :** .....

**Occupation :**..... **Date**

**:**.....

**Address :**.....

#### **Presenting Complaint**

**:**.....

.....

.....

**Duration of Hypertension :**.....(year)

#### **Treatment History**

**:**.....

.....

.....

#### **Past History :**

**Diabetes mellitus**.....

**/ IHD**.....

**/ Stroke**.....

#### **Family History :**

**Diabetes mellitus**..... /

**IHD**.....

**Stroke**.....

#### **Personal History :**

**Tobacco**.....yes| no



- Smoking : Yes/No  
 Quantity :.....  
 Duration :.....  
 Alcohol Consumption : Yes/No  
 Duration :.....  
 Diet : Veg/Non-Veg  
 Menstrual History :.....  
 General Physical Examination :  
 Pallor.....  
 Clubbing.....  
 Oedema.....  
 Cyanosis.....  
 Icterus.....  
 Xanthoma.....  
 Arcus senilis.....  
 Tophi.....  
 Arthritis.....  
 Pulse : Rate : /min.  
 Rhythm :.....  
 Character :.....  
 Volume :.....  
 Condition of vessel wall:.....  
 Other peripheral pulses:.....  
 BP (Sitting) : 1. mm Hg (Standing) : 1. mm Hg  
 2. mm Hg. 2. mm Hg  
 3. mm Hg 3. mm Hg  
 Respiratory rate: /min Temperature : 0 F  
 Height :.....cms.  
 Weight :..... Kgs  
 BMI :.....

## Annex (2) Consent:

### Informed Consent

We would like to invite you to participate in a research study. You are free to participate and all information you will provide will be confidential and anonymous,

**Things you should know:**

- ***The purpose*** of this study is to measure the uric acid levels in hypertensive patients. If you agree on participating we will ask some questions that will be confidential.
- ***Your participation*** in this research will contribute to identify the risk factors related to your condition and will help in the management and prevention of the disease you are suffering from.
- ***Your confidentiality*** will be ensured by the use of an anonymous research tool and the data will not be used for any other purpose rather than the research objectives. It is possible that other people may need to see the information we collected about you, these people work for the International University of Africa and State Ministry of Health that are responsible for making sure the research is done safely and properly. The study results will be published to arise national and international awareness of the public health problem of your disease and we ensure you that any information collected will not enable your direct identification.
- ***Your right***. It is totally up to you to decide to be in this study. Participation is voluntary. You will be given the privilege to answer only the questions you want and also to withdraw from the study at anytime you wish.
- ***For any further question*** you may have about this research, feel free to contact any time

**Dr: NisreenAbdulateef Saeed**, Research Author

Phone: 0919918712

Email: nisreenabdulateef99@gmail.com

By signing this document, you are agreeing to participate in this study. Make sure you understand what the study is about before you sign. If you have any question after you sign, you can contact the research team using the addresses provided above.

***I understand what the study is about and my questions have been satisfactorily answered. I agree to take part in this study.***

\_\_\_\_\_  
**Participant Name**

\_\_\_\_\_  
**Signature**

\_\_\_\_\_  
**Date**